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Response to Comment on: "Novel ligand-binding domain truncated *CPSF7::RARA::CPSF7* tripartite fusion confers primary ATRA resistance in atypical acute promyelocytic leukemia"

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Running title: Response to *STAT5B::RARA::RP11-750B16.1* fusion in APL

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Main Text

We read with sincere interest the Comment from Drs. Su and Feng describing a novel tripartite *STAT5B::RARA::RP11-750B16.1* fusion in a case of variant acute promyelocytic leukemia (APL). We greatly appreciate the authors' attention to our work, and this new finding is a valuable, well-documented addition to the growing body of research on rare RARA rearrangements in atypical APL (aAPL).

In our original paper, we reported a homotypic *CPSF7::RARA::CPSF7* tripartite fusion in an aAPL patient with primary all-trans retinoic acid (ATRA) resistance. Through functional validation, we confirmed that truncation of the retinoic acid receptor alpha (RARA) ligand-binding domain (LBD) helices 11–12 (H11-H12), driven by the 3′ fusion partner, directly abolished ATRA responsiveness. When we conducted this work, we noted that existing reports of tripartite *RARA* fusions were limited to coding gene partners and transposable elements (TEs), and we suspected that the repertoire of 3′ fusion partners was far broader than what had been documented. The case reported by the authors directly fills this gap.

This is the first report of a transcribed pseudogene serving as the 3′ partner in a tripartite *RARA* fusion, and it aligns perfectly with the core mechanistic model we and others have proposed. In this case, the 3′ fusion with *RP11-750B16.1* replaces the native 3′ end of *RARA*, resulting in loss of the LBD H12 helix. This structural change abolishes the allosteric transition required for coactivator recruitment upon ATRA binding, which explains the clinical ATRA resistance seen in this patient—exactly the same mechanism we validated in our *CPSF7::RARA::CPSF7* case.

Beyond expanding the molecular spectrum of tripartite *RARA* fusions, this work also raises important new questions about the role of pseudogenes in hematologic malignancies. *RP11-750B16.1* was previously thought to be a non-functional processed pseudogene, but its incorporation into an oncogenic fusion transcript, and prior evidence of its transcriptional activity in hematopoietic cells, suggest it may have unrecognized biological functions. It will be critical to determine whether this pseudogene contributes additional oncogenic effects beyond providing a polyadenylation signal, such as altering fusion transcript stability or mediating downstream regulatory effects.

From a clinical standpoint, this finding, together with our work, has clear implications for the diagnosis and management of variant APL. For patients with morphologically confirmed APL but negative for the classical *PML::RARA* fusion,standard targeted PCR panels that only detect 5′ *RARA* fusions will miss these tripartite rearrangements. Whole-transcriptome sequencing with full coverage of the *RARA* locus should be prioritized in this population, to identify these fusions early, predict primary ATRA resistance, and guide upfront treatment decisions.

We thank Drs. Su and Feng again for sharing this important case, which complements and extends our work, and deepens our understanding of the molecular pathogenesis of aAPL.

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